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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,717	03/12/2001	Terry B. Storm	01948-051003	2953

26161 7590 10/27/2003

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	22

DATE MAILED: 10/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,717	STORM ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003 and 20 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendments received on 3/13/03 and 5/20/03 have been entered. Claims 51-55 are currently pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

It is noted that the applicant's petition to accept an unintentionally delayed claim under 35 U.S.C. 120 for benefit of priority to prior application 09/304,755 was granted on 5/21/03. It is further noted that the applicant has amended the first paragraph of the specification to include a specific reference to parent application 09/304,755. In view of the petition decision and amendment to the specification, the office acknowledges that the instant application receives the benefit of priority to parent application 09/304,755.

Based on the requirements of U.S.C. 120 and 37 CFR 1.78(a)(1) and (a)(2), the subject matter of claims 51-53 is granted benefit of priority to the filing date of parent application 07/843,731, 2/28/92.

However, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 for the subject matter of claims 54-55 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Parent application 07/843,731 fails to disclose or provide an adequate written description for nucleic acid molecules encoding TGF-β or IL-10. Therefore, the priority date for applicant's claims 54-55 is the filing date of parent application 08/024,569, 3/1/93.

Claim Rejections - 35 USC § 102

The rejection of claims 51-55 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,958,403 (9/23/99), hereafter referred to as the '403 patent, is **withdrawn** in view of applicant's amendment to the specification and petition under 37 CFR 1.78(a)(3).

Double Patenting

> The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 51-53 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,958,403, the '403 patent as noted above. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed invention fully encompasses claim 1 of U.S. Patent No. 5,958,403.

Claim 1 of the '403 patent is a species of the instant claims 51-53. Claim 51 of the instant application recites a method of inhibiting the rejection of a cell transplanted into a human patient, comprising introducing a DNA construct comprising a DNA molecule encoding an immunosuppressive polypeptide into the cell and transplanting the cell into a patient. Claim 1 of the '403 patent recites a species of the broader method recited in claim 51 of the instant application as Claim 1 of the '403 patent is limited to islet cells and an immunosuppressive

polypeptide which is CTLA4-Ig. Please note as well that although claim 1 does not specifically recite that the cell is allogeneic or xenogeneic, the specification of the '403 patent clearly teaches these two embodiments as the preferred embodiments of the methods as claimed. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978). Thus, the species claimed in claim 1 of the '403 patent renders the genus claims of claims 51-53 in the instant application obvious.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-55 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the rejection of an islet cell transplanted into a human patient comprising a) introducing into an islet cell *ex vivo* a nucleic acid sequence encoding CTLA4-Ig operably linked to a promoter, wherein the CTLA4-Ig is expressed by the islet cells, and b) transplanting the islet cell into the patient, wherein CTLA4-Ig is expressed at a level sufficient to inhibit the rejection of the transplanted cell, does not reasonably provide enablement for a method of inhibiting the rejection of cells other than islet

cells or for methods which utilize constructs which encode immunosuppressive polypeptides other than CTLA4-Ig. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The applicant's claims recite the following subject matter which is not fully enabled by the specification: methods of inhibiting the rejection of a cell transplanted into a human patient, comprising introducing a DNA construct comprising a DNA molecule encoding an immunosuppressive polypeptide into the cell and transplanting the cell into a patient, wherein the immunosuppressive polypeptide is expressed at a level sufficient to suppress the rejection of the transplanted cell. The applicant further claims said methods wherein the immunosuppressive polypeptide is TGF-β or IL-10, or wherein the cells are allogeneic or xenogeneic.

The specification fails to provide an enabling disclosure for the use of immunosuppressive polypeptides other than CTLA4-Ig to prevent transplantation rejection of islet cells or any other type of cell in a patient. The specification generally discloses the introduction of DNA encoding an immunosuppressive polypeptide into cells prior to transplant in order to reduce transplant rejection. Specifically, the specification discloses nucleic acid vectors encoding CTLA4-Ig, IL-10, and TGF-β. While the specification provides a prophetic example, example 21, which outlines a method for isolating cDNA or genomic DNA encoding the putative IS-2.15 suppressor factor, no actual nucleic acid sequence is

disclosed. The working examples provided disclose the retroviral delivery of cytokines to murine epithelial cell *ex vivo* and the detection of gene expression when the cells are placed under the renal capsule. Other examples describe an allogeneic transplant model, also involving placement of cells under the renal capsule, which could be used to test for the efficacy of immunosuppressive agents. Examples 15-20 disclose that the supernatant of IS-2.15 T cells is capable of inhibiting Il-2 dependent growth of murine T-cell lines. However, no actual protein present in the IS-2.15 T cell supernatant is disclosed which has the alleged immunosuppressive activity. In sum, the working examples provide a model for testing the efficacy of immunosuppressive agents and some evidence that transfected cells placed under the renal capsule are capable of expressing an encoded polypeptide, but no actual evidence that the rejection of allogeneic or xenogeneic cells can be prevented by transfecting the cells *ex vivo* or *in vivo* with DNA encoding an immunosuppressive agent such as IL-10 or TGF-β.

The state of the art of transplantation at the time of filing suggests that prevention of allograft or xenograft rejection was not considered routine or predictable. For example, Sanberg et al. teaches that, "[p]erhaps the most serious problem faced in the field of cell transplantation is that of host generated immune response to the grafted tissue. The prevailing strategy is to systemically immunosuppress the transplanted patient for extended periods of time. This, however, puts the patient at risk for other health problems" (Sanberg et al. (1998) Nuc. Acids. Symp., Vol. 38, 139-142). Without potent immunosuppressive therapy, foreign tissue is rapidly rejected by the host mammal's immune system. Rejection is mediated

by cytotoxic CD8 +T cells, CD4+ T cells, NK cells, and antibody-dependent cellular cytotoxicity. (Kaufman et al. (1995) Annu. Rev. Immunol., Vol. 13, pages 342-343). In the case of xenogeneic tissue, hyperacute rejection of xenogeneic tissues mediated by preformed antibodies can occur in as little as 2 hours, (Kaufman et al., supra, pages 339-367). While the applicant has shown that cells transformed with a retrovirus encoding a cytokine are capable of expressing that cytokine *in vivo*, the mere exemplification of expression of a polypeptide *in vivo* does not suggest that the same level of expression or immune response generated would inhibit graft rejection, particularly since the site of cell transplantation used by applicants is not orthotopic. Transplantation of islet cells or epithelial cells under the renal capsule is not a natural location for these cells types. Furthermore, Morris teaches that at the time of filing, "..cytokines, the messages involved in the cellular interactions of the immune response, are of key importance in the alloresponse, but there is little or no information concerning their role in cell transplants.. " (Morris(1993) Cell Transplantation, Vol. 2, 7-12, see page 9), second column , second paragraph). Morris also states that, "the major obstacle to the suppression of the immune response to allogenic cells is the lack of knowledge of the mechanism of rejection of cellular transplants, which is likely to be different to that of a vascularized organ allograft, and also is likely to be dependent on the site of implantation of the cell transplant" (Morris, page 10, column 1, last paragraph). Thus, in view of the art recognized unpredictability of cytokines on graft rejection, and the unpredictability associated with preventing allograft and xenograft rejection at the time of filing, the skilled artisan would not be able to predict from

applicant's expression data whether the achieved level of expression of any particular cytokine from any type of cells placed under the renal capsule would have any effect on the rejection of the transplanted cells.

In regards to IL-10 and TGF-β in particular, the specification does not provide any evidence that these cytokines are capable of inhibiting the rejection of transplanted cells. Further, at the time of filing, the skilled artisan did not consider IL-10 or TGF-β as immunosuppressive for allograft or xenograft transplantation. Lee et al. discloses that pancreatic expression of TGF-β did not delay allograft rejection, nor did it inhibit autoimmune diabetes after lymphocytic choriomeningitis infection of double transgenic mice (LCMV/TGF-β1 mice) (Lee et al. (1996) Transplantation, Vol. 61(7), 1112-1125). Lee et al. concluded that local TGF-β does not serve as an immunosuppressive agent for allograft rejection or virus-mediated autoimmune disease (Lee et al., abstract). Lee et al. also teaches that the inability of local TGF-β to inhibit or delay allograft rejection is consistent with results from testing pancreatic IL-10, which also failed to abrogate allograft rejection (Lee et al., page 1113, column 2). These outcomes are contrary to expectations based on *in vitro* experiments, which indicates the important differences between experimental results in the laboratory and their application to living creatures. Bromberg et al. concurs with Lee et al., stating that although, "recent data suggest that IL-10 may play a role in the regulation of graft rejection and acceptance", "[t]he data do not, however, provide unambiguous proof for these roles" (Bromberg et al. (1995) Curr. Opin. Immunol., Vol. 7, 629-643, see page 641,

last paragraph). Therefore, based on the teachings of the prior art regarding the failure of IL-10 or TGF-β to inhibit graft rejection, and the lack of evidence in the specification to the contrary, the skilled artisan would not have predicted that either IL-10 or TGF-β would be capable of inhibiting cell transplant rejection.

In conclusion, based on the state of the art of transplantation rejection at the time of filing, the state of the art of cytokine therapy of graft rejection, the lack of correlation between applicant's working examples and any effect on transplant rejection, and the breadth of the claims, it would have required undue experimentation to practice the full scope of the invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER